CYP2D6: citalopram/escitalopram 1998/1999/2000

95% CI = 95% confidence interval, AUC = area under the concentration-time curve, Cl_{or} = oral clearance, C_{ss} = plasma concentration in steady state, CT = citalopram, EM = extensive metaboliser (gene dose 1.5-2.5) (normal CYP2D6 enzyme activity), IM = intermediate metaboliser (gene dose 0.5-1) (reduced CYP2D6 enzyme activity), ln = natural logarithm, MR = metabolic ratio, NS = non-significant, OR = odds ratio, PM = poor metaboliser (gene dose 0) (absent CYP2D6 enzyme activity), S = significant, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (gene dose ≥ 3) (increased CYP2D6 enzyme activity).

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Citalopram is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4. There is insufficient evidence to support a CYP2D6-(es)citalopram interaction (no/no-interactions).
None of the five studies investigating side effects found a significant effect of the CYP2D6 phenotype (Han 2013, Mrazek 2011, Peters 2008, Grasmader 2004 and Sindrup 1993). Of the four studies investigating efficacy, two large studies did not find an effect of the CYP2D6 phenotype (Mrazek 2011 (n = 1235) and Peters 2008 (n = 1953)). In addition, the two small studies contradicted each other. Han 2013 (n = 94) found a decrease in efficacy in patients with reduced CYP2D6 enzyme activity (intermediate metabolisers (IM)) and Tsai 2010 (n = 98) an increase. Both the small size of these studies and the contradictory result, suggest the results of these studies to be chance findings. Only four of the ten kinetic studies found a significant effect of reduced or absent CYP2D6 enzyme activity (intermediate or poor metaboliser (IM or PM)) on the plasma concentration or AUC of (es)citalopram (Chen 2013, de Vos 2011, Fudio 2010 and Herrlin 2003). The effect was small in all four of these studies; an increase by 20-24% for IM and a decrease of S-citalopram by 15% for PM.
You can find a detailed overview of the observed kinetic and clinical consequences per phenotype in the background information text of the gene-drug interactions on the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The table below follows the KNMP definitions for EM, PM, IM and UM. The definitions of EM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1 - citalopram
Chen B et al.
Estimation of CYP2D6*10 genotypes on citalopram disposition in Chinese subjects by population pharmacokinetic assay.
J Clin Pharm Ther 2013;38:504-11.
PubMed PMID: 23981149.</td><td>3</td><td>23 healthy volunteers, selected for the absence of the CYP-2C19 poor metaboliser phenotype, received a single dose of 20 mg citalopram on two separate occasions. Co-medication was excluded.

Genotyping:
- 4x *1/*1 (2x CYP2C19 *1/*1, 2x CYP2C19 *1/*2)
- 7x *1/*10 (2x CYP2C19 *1/*1, 5x CYP2C19 *1/*2)
- 12x *10/*10 (5x CYP2C19 *1/*1, 7x CYP2C19 *1/*2)

Results:
<table>
<tr><td colspan="5">Results versus *1/*1:</td></tr>
<tr><td></td><td>CYP2-C19 genotype</td><td>*10/*10</td><td>*1/*10</td><td>value for *1/*1</td></tr>
<tr><td rowspan="2">AUC citalopram</td><td>all</td><td>x 1.55 (NS)</td><td>x 1.33 (NS)</td><td>1175</td></tr>
<tr><td>*1/*1</td><td>x 1.21 (NS)</td><td>x 1.15 (NS)</td><td>1175</td></tr>
</table></td><td>Authors’ conclusion:
‘CYP2C19 and CYP2D6 genotypes have impacts on the CL/F of citalopram.’

AUC citalopram versus *1/*1 (for patients with CYP-2C19 *1/*1, which is the large majority in the Netherlands):
IM: 121%</td></tr>
</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td>IM: AA</td>
<td>
<table>
<tr><td>(ng.h/ml)</td><td>*1/*2</td><td>x 1.79 (NS)</td><td>x 1.41 (NS)</td><td>1175</td></tr>
<tr><td rowspan="3">Cl_{or} (L/h)</td><td>all</td><td>x 0.68 (S)</td><td>x 0.74 (S)</td><td>17.5</td></tr>
<tr><td>*1/*1</td><td>x 0.83 (NS)</td><td>x 0.85 (NS)</td><td>17.5</td></tr>
<tr><td>*1/*2</td><td>x 0.57 (NS)</td><td>x 0.70 (NS)</td><td>17.6</td></tr>
<tr><td colspan="5">Significance versus *1/*1 was only determined for Cl_{or} for all patients.</td></tr>
<tr><td colspan="5">In pharmacokinetic modelling, only the combination of the CYP2C19 and CYP2D6 genotypes was found to be a significant predictor of Cl_{or}.</td></tr>
</table>

NOTE: Genotyping was for *10. This is the most important gene variant in this Chinese population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 2 - escitalopram
Han KM et al. CYP2D6 P34S polymorphism and outcomes of escitalopram treatment in Koreans with major depression. Psychiatry Investig 2013;10:286-93. PubMed PMID: 24302953.</td>
<td>3

IM: C</td>
<td>
94 patients with major depressive disorder were treated with escitalopram 5-40 mg/day for 12 weeks. Patients with a score of at least 18 on the 21-item Hamilton Depression Rating scale (HAMD-21) were included. 56 patients completed the study and 38 patients withdrew because of a failure to draw blood, lack of efficacy, personal conflict or other personal decision, loss to treatment, or adverse events. Response was defined as a reduction of 50% or more in the HAMD-21 score. Remission was defined as a HAMD-21 score of 7 points or less. The side-effects profile was assessed using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (UKU-SERS).
Other psychotropic drugs, such as antipsychotics and mood stabilizers were excluded, but CYP2D6 inhibitors or inducers were not.
Multiple logistic regression analysis with sex and age as covariates was used to investigate the association of *10 with treatment efficacy.

Genotyping:
- 28x *1/*1
- 38x *1/*1*10
- 28x *10/*10

Results:
<table>
<tr><td colspan="4">Results for *10/*10 versus *1/*10 versus *1/*1:</td></tr>
<tr><td></td><td></td><td>OR (95% CI)</td><td>value for *1/*1</td></tr>
<tr><td rowspan="6">% of patients with remission</td><td>1 week</td><td>NS</td><td>7.4%</td></tr>
<tr><td>2 weeks</td><td>NS</td><td>13%</td></tr>
<tr><td rowspan="2">4 weeks</td><td>trend for a decrease (p = 0.055) (NS)</td><td rowspan="2">36%</td></tr>
<tr><td>Also a trend for a decrease (p = 0.054) (NS) for *10/*10 versus *1/*1+ *1/*10.</td></tr>
<tr><td rowspan="2">8 weeks</td><td>0.38 (0.15-0.98) (S)</td><td rowspan="2">32%</td></tr>
<tr><td>0.12 (0.01-0.90) (S) for *10/*10 versus *1/*1+ *1/*10.</td></tr>
<tr><td rowspan="2">12 weeks</td><td>0.36 (0.16-0.81) (S)</td><td rowspan="2">53%</td></tr>
<tr><td>0.12 (0.02-0.61) (S) for *10/*10 versus *1/*1+ *1/*10.</td></tr>
<tr><td rowspan="3">% of responders</td><td>1 week</td><td>NS</td><td>11%</td></tr>
<tr><td rowspan="2">2 weeks</td><td>NS</td><td rowspan="2">33%</td></tr>
<tr><td>Trend for a decrease (p = 0.099) (NS) for *10/*10 versus *1/*1+*1/*10.</td></tr>
</table>
</td>
<td>Authors' conclusion:
'Our results suggest that the P allele of the CYP-2D6 P34S polymorphism is a favorable factor in escitalopram treatment for MDD, and that the CYP2D6 P34S polymorphism may be a good genetic marker for predicting escitalopram treatment outcomes.'</td>
</tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td></td>
<td>
<table>
<tr><td></td><td>4 weeks</td><td>trend for a decrease (p = 0.096) (NS)
NS for *10/*10 versus *1/*1+*1/*10.</td><td>64%</td></tr>
<tr><td></td><td>8 weeks</td><td>0.45 (0.22-0.93) (S)
0.28 (0.09-0.88) (S) for *10/*10 versus *1/*1+ *1/*10.</td><td>74%</td></tr>
<tr><td></td><td>12 weeks</td><td>0.21 (0.08-0.54) (S)
0.09 (0.02-0.34) (S) for *10/*10 versus *1/*1+ *1/*10.</td><td>88%</td></tr>
<tr><td>escitalopram-induced side effects</td><td>psychic</td><td>NS</td><td></td></tr>
<tr><td></td><td>sleep</td><td>NS</td><td></td></tr>
<tr><td></td><td>extrapyramidal</td><td>NS</td><td></td></tr>
<tr><td></td><td>gastrointestinal</td><td>NS</td><td></td></tr>
<tr><td></td><td>autonomic</td><td>NS</td><td></td></tr>
<tr><td></td><td>skin</td><td>NS</td><td></td></tr>
<tr><td></td><td>hormonal</td><td>NS</td><td></td></tr>
<tr><td></td><td>sexual</td><td>NS</td><td></td></tr>
<tr><td></td><td>headache</td><td>NS</td><td></td></tr>
</table>
NOTE: Genotyping was for *10. This is the most important gene variant in this Korean population.
</td>
<td></td>
</tr>
<tr>
<td>ref. 3 - escitalopram
Huezo-Diaz P et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. J Psychopharmacol 2012;26:398-407. PubMed PMID: 21926427.</td>
<td>3

PM: AA
IM: AA
UM: AA</td>
<td>194 patients were treated with escitalopram 10-30 mg/day.

Genotypes/phenotypes:
- 91x EM (63x gene dose 2; 28x gene dose 1.5)
- 82x EM (67x gene dose 1; 14x gene dose 0.5; 1x *17/null allele)
- 14x PM
- 7x UM

Blood samples were collected 1-4 hours after taking the daily dose. A total of 7 patients used CYP2D6 inhibitors, but correction was performed for co-medication.

Gene dose 0.5 versus gene dose 2:
- increased ln(C_{ss}[a] escitalopram) from 0.44 to 0.91 μg/L per mg (S)
- this corresponds to an increase in C_{ss}[a] escitalopram by 60% (from 1.55 to 2.48 μg/L per mg) (S)
- decrease in the ratio of escitalopram/desmethylescitalopram by 34% (from 0.41 to 0.27) (S)

Other gene doses versus gene dose 2:
- no significant differences in ln(C_{ss}[a] escitalopram) and the metabolic ratio (NS)

NOTE: Genotyping for *3 through *11, *14A, *15, *17, *19, *20, *29, *36, *40, *41 and gene duplication (*1, *2 and *35).</td>
<td>Authors' conclusion:
"Subjects who had one CYP2D6 allele associated with intermediate metabolizer phenotype and one associated with poor metabolizer (i.e. IM/PM genotypic category) had a higher mean logarithm escitalopram concentration than CYP2D6 extensive metabolizers (EMs)."</td>
</tr>
<tr>
<td>ref. 4 - citalopram
de Vos A et al. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients.</td>
<td>3</td>
<td>Routine therapeutic drug monitoring was performed on 338 patients being treated with citalopram.

Genotypes/phenotypes:
- 170x EM (*1/*1)
- 127x IM (gene dose 1)
- 34x PM (gene dose 0)
- 7x UM (gene dose ≥ 3)</td>
<td>Authors' conclusion:
"Significant association of CYP2D6 genotype with citalopram metabolism was observed."</td>
</tr>
</table>

Pharmacogenomics J 2011;11:359-67. PubMed PMID: 20531370. **ref. 4, continuation**	IM: A PM: AA UM: AA	The citalopram dose was known for 223 patients (111x EM, 81x IM, 26x PM, 5x UM). Relevant co-medication was not excluded. IM versus EM: - increase in the dose by 14% (from 28 to 32 mg/day) (S) - increase in the dose-corrected C_{ss} citalopram by 20% (from 2.5 to 3.0 µg/L per mg/day) (S) - increase in the ratio of citalopram/desmethylcitalopram by 19% (from 2.6 to 3.1) (S) PM versus EM: - no difference in dose (both 28 mg/day) (NS) - increase in the dose-corrected C_{ss} citalopram by 16% (from 2.5 to 2.9 µg/L per mg/day) (NS) - decrease in the ratio of citalopram/desmethylcitalopram by 7.7% (from 2.6 to 2.4) (NS) UM versus EM: - no significant difference in dose (24 versus 28 mg/day) (NS) - decrease in the dose-corrected C_{ss} citalopram by 16% (from 2.5 to 2.1 µg/L per mg/day) (NS) - decrease in the ratio of citalopram/desmethylcitalopram by 12% (from 2.6 to 2.3) (NS) NOTE: Genotyping for *3 through *6 and gene duplica-tion.	Plasma concen-tration versus EM: IM: 120% PM: 116% UM: 84%
ref. 5 - citalopram Mrazek DA et al. CYP2C19 variation and citalopram response. Pharmacogenet Genomics 2011;21:1-9. PubMed PMID: 21192344.	3 IM: AA PM: AA UM: AA	1235 white patients without Latin-American, Portuguese or Spanish ancestry were treated with citalopram 20-60 mg/day. Genotypes/phenotypes: - 36% EM (gene doses 2 and 2.5) - 44% gene doses 1 or 1.5 - 13% PM or gene dose 0.5 - 6% UM (gene dose ≥ 3) A total of 1074 patients used citalopram for at least 6 weeks. Co-medication with an effect on CYP2D6 was not excluded. CYP2D6 genotypes: - were non-significantly associated with tolerance (NS). Intolerance was defined as leaving the study, or not conti-nuing with citalopram at the end of the study due to adver-se events. - were non-significantly associated with remission (NS). Remission was defined as a score ≤ 5 on the 16-item Quick Inventory of Depressive Symptomatology – Clinical Rating. NOTE: Genotyping for *2A, *2 through *12, *14, *17, *41 and gene duplication. NOTE: The assignment of gene dose 0.5 to *2 and gene dose 1.5 to *2A differs from our system (gene dose 1 for *2).	Authors' conclu-sion: "No relationship between CYP2D6 genotype-based categories and either remission or tolerance was identified."
ref. 6 - escitalo-pram Tsai MH et al. Genetic polymor-phisms of cytochro-me P450 enzymes influence metabo-lism of the antide-pressant escitalo-	3	A total of 98 patients were treated with escitalopram (4 weeks 10 mg/day, followed by 4 weeks 10-30 mg/day). Genotypes/phenotypes: - 57x EM (16x gene dose 2; 41x gene dose 1.5) - 41x IM (12x gene dose 0.5; 29x gene dose 1 (of which 26x *10/*10)) Co-medication with an effect on CYP2D6 was not excluded.	Authors' conclu-sion: "The group of patients with gene dose 0.5 had a significantly higher frequency of remit-ters from major depressive disorder

pram and treatment response. Pharmacogenomics 2010;11:537-46. PubMed PMID: 20350136. **ref. 6, continuation**	IM: AA	Remission was defined as less than 10 points on the Hamilton Depression Scale (HAM-D; maximum score of 21 points). Upon inclusion, the patients had a score ≥ 14 on the HAM-D (mean 22.14). - no difference in dose and C_{ss} of escitalopram and metabolites between the various allele combinations - no difference in C_{ss} of escitalopram and desmethylescitalopram between gene dose 0.5 and gene doses 1 through 2 - higher percentage of patients with remission for gene dose 0.5 compared to gene doses 1 through 2 (100% versus approx. 70%) (S) NOTE: Genotyping for *4, *5, *10 and gene duplication. These are the most common polymorphisms in this (ethnically Chinese) population.	during the 8-week treatment. However, serum concentrations of S-CIT, S-DCIT or the S-DCIT:S-CIT ratio in the patients at 0.5 gene dose of CYP2D6 were not shown to be significantly higher than the non-0.5 gene dose groups over the 8-week treatment course."
ref. 7 - citalopram Fudio S et al. Evaluation of the influence of sex and CYP2C19 and CYP-2D6 polymorphisms in the disposition of citalopram. Eur J Pharmacol 2010;626:200-4. PubMed PMID: 19840783.	3 IM: A	In a cross-over study, 35 healthy volunteers (27x EM, 8x IM) received a single dose of 20 mg citalopram. The formulation of citalopram varied between the two parts of the study. Co-medication, smokers and alcohol consumption were excluded. Raw data are not provided, only data predicted using a pharmacokinetic model. IM versus EM: - increase in the predicted AUC^b by 23.7% (from 3112.7 to 3851.6 ng.hour/mL per mg/kg) (S) - decrease in the predicted $Cl_{or}{}^a$ by 16.1% (from 6.27 to 5.26 mL/min per kg) (S) IM versus EM for volunteers who are CYP2C19 *1/*1 (n=26): - no significant increase in the predicted AUC^b (NS) IM versus EM for volunteers who are CYP2C19 *1/*2 (n=7): - increase in the predicted AUC^b by approx. 60% (from approx. 2500 to approx. 4000 ng.hour/mL per mg/kg) (S) NOTE: The percentage CYP2C19 *1/*2 is greater for IM than for EM (37.5% versus 14.8%). Therefore, in this study, it appears that the genotypes are not independent. NOTE: Genotyping was only performed for *4.	Authors' conclusion: "CYP2D6 volunteers carrying *1/*4 have an AUC 23% higher than wild type. Our data also suggest that the influence of CYP-2D6 on AUC_∞ is very low when it is in association with CYP2C19 *1/*1 while its influence is more apparent in association with CYP2C19*1/*2." AUC citalopram versus EM: IM: 124%
ref. 8 - citalopram Peters EJ et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. PLoS One 2008;3:e1872. PubMed PMID: 18382661.	3 IM: AA PM: AA	The same study as in Mrazek DA et al., 2009, but here analysis of the data was performed for all Caucasian and African-American patients. A total of 1953 patients, who were treated with citalopram 20-60 mg/day, were divided over two case-control studies (research study (n=831) and validation study (n=1046)). Co-medication with an effect on CYP2D6 was not excluded. The study lasted 12 weeks. Only patients who used citalopram for more than 6 weeks were used in analysis of response parameters. Caucasian and African-American patients were analysed separately. CYP2D6 gene doses: - were non-significantly associated with tolerance (NS). Intolerance was defined as leaving the study, or not continuing with citalopram at the end of the study due to adverse events. - were non-significantly associated with response (NS). Response was defined as a reduction in the score on the 16-item Quick Inventory of Depressive Symptomatology (Self Report version) (QIDS-SR) by 50%.	Authors' conclusion: "No genetic polymorphism in the pharmacokinetic genes examined was significantly associated with our response or tolerance phenotypes in both stages."

ref. 8, continuation		- were non-significantly associated with remission (NS). Remission was defined as a score ≤ 5 on the QIDS-SR. PM versus (EM+IM+UM): - no significant difference in tolerance and response (NS) - no significant decrease in the dose (NS) - no significant difference in the duration of use of citalopram (NS) NOTE: Genotyping for *3 through *9.	
ref. 9 - citalopram Grasmader K et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. Eur J Clin Pharmacol 2004;60:329-36.	3 PM: AA	Genotyping was performed on 136 patients on antidepressants, including 15 patients on citalopram (dose unknown). Out of the 15 patients on CT, 2 were CYP2D6 PM, the other 13 patients were either CYP2D6 IM or EM. Co-medication was permitted. The median dose-corrected C_{ss} was 1.60 ng/mL per mg of dosed CT. For the two PMs, the corrected plasma concentration was 70% and 39% higher than the median. Both experienced relevant side effects.	Plasma concentration versus EM + IM: PM: 155%
ref. 10 - citalopram Herrlin K et al. Metabolism of citalopram enantiomers in CYP2C19/CYP-2D6 phenotyped panels of healthy Swedes. Br J Clin Pharmacol 2003;56:415-21.	3 PM: A	12 healthy volunteers (6x EM, 6x PM; all CYP2C19 EM) received citalopram 20 mg/day for 7 days, no relevant co-medication; PM versus EM: - decrease in AUC of racemic mixture from 1398 to 1392 nM/h (by 0.4%, significance unknown) - decrease in AUC S-CT from 530 to 451 nM/h (S by 15%). - no significant difference for AUC R-CT. - increase in AUC S-desmethyl-CT from 208 to 237 nM/h (NS by 14%) and for R-desmethyl-CT from 233 to 251 nM/h (NS by 8%). - decrease in AUC didesmethyl-CT from 96 nM/h to below the quantification limit (S by 100%) NOTE: Genotype unknown.	AUC citalopram versus EM: PM: 100% AUC S-citalopram versus EM: PM: 85%
ref. 11 - citalopram Carlsson B et al. Enantioselective analysis of citalopram and metabolites in adolescents. Ther Drug Monit 2001;23:658-64.	4 IM: AA UM: AA	19 adolescents (14x EM, 3x IM, 2x UM) were treated with citalopram 10-60 mg/day. Co-medication other than oral contraception is rare. A total of 53% were smokers. IM versus EM: - decrease in C_{ss}[a] racemic mixture from 5.97 to 4.82 nmol/L per mg (significance unknown, by 19%) - decrease in C_{ss}[a] S-CT from 2.21 to 1.65 nmol/L per mg (significance unknown, by 26%) - decrease in C_{ss}[a] R-CT from 3.76 to 3.17 nmol/L per mg (significance unknown, by 16%) UM versus EM: - decrease in C_{ss}[a] racemic mixture from 5.97 to 2.58 nmol/L per mg (significance unknown, by 57%) - decrease in C_{ss}[a] S-CT from 2.21 to 0.94 nmol/L per mg (significance unknown, by 58%) - decrease in C_{ss}[a] R-CT from 3.76 to 1.54 nmol/L per mg (significance unknown, by 59%)	C_{ss}[a] citalopram versus EM: IM: 81% UM: 43% C_{ss}[a] S-citalopram versus EM: IM: 74% UM: 42%

ref. 11, continuation		NOTE: Genotyping was performed for the alleles *3, *4 and *6 and for gene duplication.	
ref. 12 - citalopram Bondolfi G et al. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. Psychopharmacology 1996;128:421-5.	3 PM: AA	7 female patients (6x EM, 1x PM; all CYP2C19 EM) were first treated with citalopram 40 mg/day for 3 weeks, followed by the addition of fluvoxamine 50 mg/day for 3 weeks. Benzodiazepines, chloralhydrate and non-relevant co-medication were permitted. PM: - C_{ss} citalopram and desmethylcitalopram were within the range observed for the other patients. NOTE: Genotype unknown.	
ref. 13 - citalopram Sindrup SH et al. Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. Ther Drug Monit 1993;15:11-7.	3 PM: A	24 healthy volunteers received citalopram 40 mg/day for 10 days. The data of 18 volunteers (10x EM, 8x PM; all CYP2C19 EM) were presented. PM versus EM: - increase in AUC citalopram from median 4588 to 4700 nM.hour (NS, by 2%) - increase in $t_{1/2}$ from median 30 to 36 hours (NS, by 20%) - increase in AUC desmethylcitalopram from median 1768 to 2400 nM.hour (S, by 36%) - decrease in AUC didesmethylcitalopram from median 370 nM.hour to undetectable (S, by 100%) - no difference in type or frequency of adverse events Citalopram is a weak inhibitor of CYP2D6. NOTE: Genotype unknown.	AUC citalopram versus EM: PM: 98%
ref. 14 - escitalopram SPC Lexapro (escitalopram) 05-09-13.	0 PM: AA	No significant difference in exposure was observed in poor CYP2D6 metabolisers.	
ref. 15 - citalopram SPC Cipramil (citalopram) 01-04-17.	0 PM: AA IM: AA UM: AA	*In vivo* research has demonstrated that the metabolites of citalopram do not exhibit any clinically relevant polymorphisms of sparteine/debrisoquine oxidation (CYP2D6).	
ref. 16 - escitalopram SPC Lexapro (escitalopram), USA, 04-01-17.	0 PM: AA	Steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism.	
ref. 17 - citalopram SPC Celexa (citalopram), USA, 04-01-17.	0 PM: AA	Citalopram steady-state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.	

[a] Corrected for dose.
[b] Corrected for dose and weight.
NOTE: Phenotyping usually does not distinguish between IM, EM and UM. Therefore, EM in these studies is usually equal to IM+EM+UM.

Risk group	-

Comments:
- Escitalopram is the S-enantiomer of citalopram, which is primarily responsible for the antidepressant and anxiolytic effect.

Date of literature search: 11 April 2018.

	Phenotype	Code	Gene-drug interaction	Action	Date
Dutch Pharmacogenetics Working Group decision	PM	4 A	No	No	14 May 2018
	IM	4 C	No	No	
	UM	4 AA	No	No	

Mechanism:
Citalopram is primarily metabolised by CYP2C19 and to a lesser extent by CYP3A4 to N-desmethylcitalopram. N-desmethylcitalopram is converted to didesmethylcitalopram by CYP2D6.
Although desmethylcitalopram has antidepressant activity, the activity is low and clinically non-significant at standard doses (Herrlin, 2003).